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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/796,307	03/10/2004	Michele Cargill	CL001509	9084

25748 7590 11/06/2006

CELERA GENOMICS
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EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/796,307	CARGILL ET AL.	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-24* is/are pending in the application.

4a) Of the above claim(s) *7-20, and 23-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date ~~10/711604~~ 4-1-05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-4 and 6-24 are currently pending. Applicant's election with traverse of Group I (Claims 1-4, 6 and 21-22) in the reply filed on September 21, 2006 is acknowledged. Applicants have further elected to have SEQ ID No 33944 searched. The traversal is on the ground(s) that at least 10 nucleotide sequences should be examined together based upon MPEP Section 803.04. This is not found persuasive because the MPEP provides for up to 10 sequences which encompasses 1 sequence. Each of the instant SNPs are patentably distinct and require an undue burden to search and consider together. The resources required to search 10 sequences has dramatically increased since the 1996 OG notice. The volume of data within the databases has grown exponentially. It is no longer reasonable for a search of 10 sequences to be performed in a single application. Moreover, the instant search does not rely solely on the computer resources, but requires a search for SNPs within a gene. Many genes have more than one name and the number of polymorphisms within the gene must be individually searched for novelty. An article which teaches polymorphisms within a gene does not necessarily use the same numbering system, or the same nomenclature. Moreover, many SNPs within Tables are not easily searchable and require burden to analyze the contents of tables within an article which have not been indexed in the database. Therefore, a search for multiples SNPs in multiple genes is an undue burden on the office. **Thus the requirement is still deemed proper and is therefore made FINAL.**

Claims 7-20 and 23-24 have withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Accordingly, Claims 1-4, 6 and 21-22 have been examined herein.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on April 1, 2005 has been considered. References which have lines drawn through them have been considered but the line has been drawn through them because there is not a publication date for those references.

Claim Objections

3. Claims 1 and 21 are objected to because claims still recite SEQ ID NOs which have not been elected. Appropriate amendments to the claims are required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-4, 6, and 21-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method for identifying an individual who has an altered risk for developing myocardial infarction comprising detecting any single nucleotide polymorphism in SEQ ID NO: 33944. The specification teaches that SEQ ID NO: 33944 is 201 base pairs in length. The specification teaches a single C/T polymorphism at position 101 of SEQ ID NO: 33944. However the claims encompass any SNP in SEQ ID NO: 33944. However the specification does not disclose and fully characterize a suffient number of SNPs that are representative of the genus required by the claims of any SNP in SEQ ID NO: 33944.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In The Regents of the University of California v. Eli Lilly (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the

court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, only one SNP in SEQ ID NO: 33944 has been identified. No additional nucleotide variations have been disclosed in the specification. Therefore the specification does not teach the complete structure of a representative number of species of the claimed genus. It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. restriction map, biological activity of an encoded protein product, etc.). In the instant case, no such identifying characteristics have been provided. Yet, the claims as written are inclusive of a potentially large genus of SNPs in SEQ ID NO: 33944. While one could contemplate a nucleotide substitution, deletion or addition at each and every position in SEQ ID NO: 33944, such nucleotide variations are not considered to be equivalent to specific nucleotide variations associated with myocardial infarctions. Rather, the mutations in SEQ ID NO: 33944 that are associated with myocardial infarctions represent a distinct group of nucleotide variations which are expected to occur at only specific locations within SEQ ID NO: 33944 and consist of specific nucleotide alterations. Accordingly, knowledge of the sequence of the wild-type gene does not allow the skilled artisan to envision all of the contemplated polymorphisms encompassed by the claimed genus. Conception of the claimed

invention cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of potential methods for isolating additional nucleotide variations. As stated in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. LTD*, 25 USPQ2d 1016, one cannot describe what one has not conceived.

For these reasons, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

5. Claims 1-4, 6, and 21-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying an individual who has an increased risk for developing myocardial infarction, comprising detecting the presence of single nucleotide polymorphism at position 101 of SEQ ID NO 33944 wherein the detection of the SNP is correlated with an altered risk for myocardial infarction, does not reasonably provide enablement for methods for identifying an individual who has an altered risk for developing myocardial infarction, comprising detecting the presence of single nucleotide polymorphism at any position of SEQ ID NO 33944 wherein the detection of the SNP is correlated with an altered risk for myocardial infarction. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn broadly to a method for identifying an individual who has an altered risk for developing myocardial infarction, comprising detecting a single nucleotide polymorphism in SEQ ID NO: 33944. Thus the claims encompass methods which detect any nucleotide variation within SEQ ID NO: 33944. The claims do not define the identity or position of any nucleotide variation within SEQ ID NO: 33944. Claim 2 further states that the SNP is associated with an increased risk for developing myocardial infarction while claim 4 further states that the SNP is associated with a decreased risk for developing myocardial infarction. Claim 3 requires that the individual has previously had a myocardial infarction. Claims 6 and 21-22 deal with methods for detecting the SNP.

Nature of the Invention

The claims are drawn broadly to a method for identifying an individual who has an altered risk for developing myocardial infarction, comprising detecting a single

nucleotide polymorphism in SEQ ID NO: 33944. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches a single C/T mutation at nucleotide position 101 of SEQ ID No 33944. The specification teaches that this mutation is a missense mutation and that it is associated with the occurrence of myocardial infarctions. It is further noted that this particular SNP is referenced as rs6685323 and hCV25753038 throughout the specification. The NCBI website teaches that rs6685323 is located on chromosome 1 within the AQP10 gene.

The specification further teaches on page 120 that to identify markers associated with myocardial infarction two case control studies were performed. One study had 1400 samples in which patients had self-reported history of myocardial infarction and the controls had no history of myocardial infarction. The second study had 1500 samples in which patients had clinical evidence of history of myocardial infarction and controls had had no history of myocardial infarction. Allele specific PCR was used to determine the allele frequencies of the SNPs. The results are shown in Table 6. Specifically for SNP hCV25753038 the odds ratio was 1.2 for the first study and 1.3 for the second study.

The specification also teaches on page 121 that to identify markers associated with recurrent myocardial infarction samples from the Cholesterol and Recurrent Events

cohort were genotyped. A well-documented myocardial infarction was a requirement to be part of the cohort. The SNP genotype frequencies of a group of 264 patients who had recurrent myocardial infarctions were compared to the SNP genotype frequencies to a group of 1255 patients who had only one myocardial infarction. The results are shown in Tables 7-8. There is no specific data provided for SNP hCV25753038.

The specification and prior art do not teach any other variations in the AQP10 gene or SEQ ID NO: 33944 that are associated with myocardial infarction. The specification further does not teach that the mutation at position 101 of SEQ ID NO: 33944 is associated with myocardial infarction in any other organisms other than humans. Additionally there are no teachings in the specification in which the mutation at position 101 of SEQ ID NO: 33944 is associated with recurrent myocardial infarctions.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of identifying novel variants in any nucleic acid sequence which are sufficiently correlated with a disease or condition that further allow for identifying an individual who has an altered risk for developing a disease or condition is highly unpredictable. Knowledge of any wild type sequence does not allow one to immediately envision any mutation in that sequence that is associated with a specific disease or condition.

The AQP10 gene is expected to contain numerous polymorphisms, particularly given the size of the gene. Thus SEQ ID NO: 33944 is also expected to contain numerous polymorphisms. However, the specification does not teach a predictable means for identifying additional variations associated with myocardial infarctions or for

distinguishing between variations associated with myocardial infarctions and naturally occurring polymorphisms. Without extensive information regarding the structure-function relationship between the AQP10 gene and myocardial infarctions, it is highly unpredictable as to what would be the identity of additional mutant, allelic, or splice variants which would be associated with myocardial infarctions. Thus, one cannot readily anticipate the effect of a polymorphism or mutation on the function or activity of the AQP10 gene or the protein encoded thereby.

Further, it is unpredictable as to whether the results obtained in human subjects could be extrapolated to other organisms. Knowledge that mutations in a gene occur in one organism (i.e. humans) does not allow one to conclude that this gene, and mutations in this gene will also occur in other organisms and will be associated with myocardial infarctions. The specification does not teach homologues of the AQP10 gene in a representative number of different organisms. The specification also does not teach any other organisms which have myocardial infarctions, such that one would expect that mutations in the homologous AQP10 genes would lead to myocardial infarctions in other organisms. This is supported by the findings of Morinaga et al (Biochemical and Biophysical Research Communication 2002) that teach that the AQP10 gene in mice is a pseudogene. Morinaga also teach that the exons of the AQP10 gene are well conserved between mouse and human but the initiator methionine is lost in mice due to a mutation at the translation initiation site. Thus it is unpredictable as to whether the AQP10 gene, and particularly the mutation at position 101 of SEQ ID

No: 33944 will also be present in other organisms and will be associated with myocardial infarctions.

It is also unpredictable as to whether the SNP at position 101 of SEQ ID NO 33944 can be used to determine ones risk of having recurrent myocardial infarctions. Just because this mutation is found in people who have had one myocardial infarction it does not mean that it can be used as an indicator for recurrent myocardial infarctions. The data in the specification is limited to an association between this mutation and the risk of developing a single myocardial infarction. There are no teachings in the specification regarding an association between this mutation and multiple myocardial infarctions.

Amount of Direction or Guidance Provided by the Specification:

The specification teaches 1 variant of SEQ ID NO 33944 which is associated with myocardial infarctions. However, the SEQ ID NO 33944 is 201 base pairs long. To identify additional variants of SEQ ID NO 33944 which are associated with myocardial infarctions would require extensive experimentation. For example, such experimentation may involve sequencing the AQP10 gene of individuals who have had myocardial infarctions, sequencing the AQP10 gene of control individuals which have not had myocardial infarctions, comparing the sequences of these two groups, and then identifying variations which are present only in the affected group and not in the control group. Such random, trial by error experimentation is considered to be undue. While methods for sequencing genes are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for mutations that may

linked to a disease. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying additional variants of SEQ ID NO 33944 and using these variants to identify individuals susceptible to myocardial infarctions.

Working Examples:

Again, the specification teaches on page 120 that to identify markers associated with myocardial infarction two case control studies were performed. One study had 1400 samples in which patients had self-reported history of myocardial infarction and the controls had no history of myocardial infarction. The second study had 1500 samples in which patients had clinical evidence of history of myocardial infarction and controls had had no history of myocardial infarction. Allele specific PCR was used to determine the allele frequencies of the SNPs. Specifically the applicants looked at the SNP at position 101 of SEQ ID NO 33994 and determined that it was associated with myocardial infarction. However there are no specific examples provided in the specification in which a subject is identified as being at risk of having a myocardial infarction by detecting any other variants of SEQ ID NO 33994. There are also no specific examples provided in the specification in which a subject is identified as being at risk of having recurrent myocardial infarctions by detecting the SNP at position 101 or any other variant of SEQ ID NO: 33994. Further, there are no working examples provided in the specification in which non-human subjects used.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification only teaches 1 mutation in SEQ ID NO: 33944 that is associated with myocardial infarctions. The specification does not teach a representative number of additional variants, including insertions, deletions, substitutions or splice variants, or gross chromosomal rearrangements which are associated with myocardial infarctions. Further, the specification does not teach how to use the mutation at position 101 of SEQ ID NO: 33944 as a means for predicting ones risk of having recurrent myocardial infarctions. Additionally, the disclosure of a single organism, humans, in which the mutation at position 101 of SEQ ID NO: 33944 is correlated with myocardial infarctions is not representative of the broadly claimed genus of any individual. Accordingly, although the level of skill in the art of molecular biology is

high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6, and 21-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4 and 6 are indefinite over the recitation of the phrase "wherein the presence of the SNP is correlated with an altered risk for myocardial infarction." Because the term "correlated" has not been clearly defined in the specification and because there is no art recognized definition for this term as it relates to a SNP and a disease, one of skill in the art cannot determine the meets and bounds of the claimed subject matter. Additionally the phrase "altered risk" encompasses an increased risk and a decreased risk. It is not clear as to how both and increase as a well as a decrease are risks for myocardial infarction.

Claims 21-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that the goal of the method and the final step do not agree. The claims are drawn to methods of detecting a single nucleotide polymorphism. However, the claims recite the final step of detecting a hybridized duplex. The steps listed in the method do

not result in the detection of a SNP. Therefore, it is unclear as to whether the claims are intended to be limited to methods for detecting a SNP or methods for detecting a hybridized duplex.

Conclusion

7. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER

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Art Unit 1634